NAVAL MEDICAL RESEARCH CENTER

NAVAL MEDICAL RESEARCH CENTER (NMRC)

To enhance the health, safety, readiness and performance of Navy and Marine Corps personnel, the Naval Medical Research Center (NMRC) and its affiliated laboratories conduct basic and applied biomedical research in infectious diseases, biological defense, combat casualty care, bone marrow, and diving and environmental medicine.

NMRC and its overseas laboratories also support global surveillance, training, research and response to emerging infectious disease threats.

Since its inception in 1942, the Naval Medical Research Institute has made many contributions to the field of military medicine, always with the focus of protecting and enhancing the health, safety, and efficiency of Navy and Marine Corps personnel.

In 1998, the Naval Medical Research Institute was closed under the Base Realignment and Closure Law, and the Naval Medical Research Center was commissioned. NMRC provides leadership for the Navy's dental and biomedical research laboratory at Great Lakes, Illinois, and for the Navy's overseas laboratories in Peru, Indonesia and Egypt.

In June 1999, along with the Walter Reed Army Institute of Research, NMRC moved to the new federal research laboratory facility, the Inouye Building, erected in the Forest Glen section of Silver Spring, Maryland.

U.S. Naval Medical Research Unit No. 2 (NAMRU-2)
Jakarta, Indonesia

U.S. Naval Medical Research Unit No. 3 (NAMRU-3)
Cairo, Egypt

Naval Medical Research Center Detachment (NMRCD)
Peru, South America

Naval Institute for Dental and Biomedical Research (NIDBR)
Great Lakes, Illinois

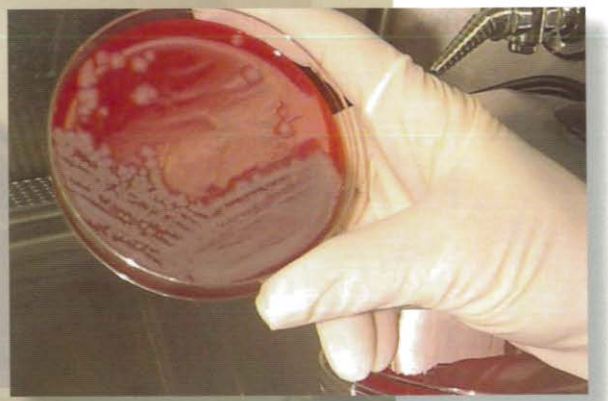
As we move into the 21st century, we face not only the medical issues associated with conventional warfare, but the potential use of weapons of mass destruction and terrorism against our military forces and our citizens. The overwhelming superiority of our defense infrastructure, where billions of dollars are invested, is vulnerable to the threat to use inexpensive asymmetric weapons of mass destruction against us.

Our research at NMRC is focused on finding solutions both to conventional medical problems on the battlefield such as bleeding, and to non-conventional weapons such as thermobaric blast, biological agents, or radiation. Research is being conducted in the fields of Infectious Diseases, Biological Warfare Defense, Dental Research and Combat Casualty Care.

Our overseas laboratories play an instrumental role in the worldwide monitoring of new emerging infectious diseases, such as SARS, that threaten both deployed forces and the world. The threatened deliberate use of biological agents as weapons in the future may require infectious diseases to be classified as battlefield related, and will be extremely serious to the unprepared. As you will see in the following excerpts, our medical research efforts are aimed at providing solutions to future medical readiness for what lies ahead on the battlefield, at sea, and at home.

Richard B. Oberst
Captain, Medical Service Corps

Biological Defense



U.S. military medical researchers have focused on how to defend the threat of biological and chemical warfare since World War I. With recent conflicts and terrorist attacks, the threat of bioterrorism has quickly risen to the consciousness of the general public.

For nearly 15 years, the Biological Defense Research Directorate (BDRD) at NMRC has researched ways to protect military personnel in the event of a biological attack. They have become a leader in the field in detection, including hand-held assays, molecular diagnostics, and confirmatory analysis. More recently, NMRC researchers have made great strides in developing a new DNA-based vaccine to protect against anthrax.

These hand held assays provide rapid screening of environmental samples, and can detect more than 20 agents.

Identifying and Studying Bio-warfare Threats

BDRD pioneered the development of small hand-held assays that identify most of the common biological threats, including anthrax. The DoD, FBI and the Secret Service routinely use these assays, which identify the biological agent within 15 minutes. These assays were selected by the Joint Program Office for Biological Defense as the standard assay produced for the DoD.

Scientists at NMRC also developed real-time Polymerase Chain Reaction (PCR) based diagnostics for confirmatory testing. These confirmatory assays are based on the DNA sequence of a particular biological agent. BDRD's anthrax assays are the standard assays for the Centers for Disease Control and Prevention. The final step in the confirmation process, definitive testing, can then be done at the NMRC laboratories in their Bio-Safety Level 3 facility.

The first portable laboratory capable of conducting molecular detection was developed by the BDRD in 1991. This unique laboratory allows military personnel in the field to quickly conduct confirmatory assays to see if biological agents are present. It was deployed in Desert Storm/Desert Shield, and similar capabilities were deployed in Operation Iraqi Freedom. The portable lab currently weighs approximately 1,000 pounds, and requires three people to run it. It can be checked onto commercial airlines, and requires only gas and motor oil to operate. The portable laboratory holds supplies sufficient to process about 150 samples, with PCR and ELISA testing. It also includes protective gear for the personnel, a generator, a freezer, and field lighting and field UPS.

In a related area of research, scientists are also working on the development of a more sensitive diagnostic field test to quickly see if humans have been exposed to biological agents. This would be especially helpful in combat situations where it is difficult to move a full field laboratory. The sooner an exposure is detected, the sooner treatment can begin. Identifying anthrax is difficult, especially in field conditions, where equipment and technologies are limited.

Two of BDRD's portable laboratories were deployed to Iraq in early 2003, available to detect biological agents in the field.

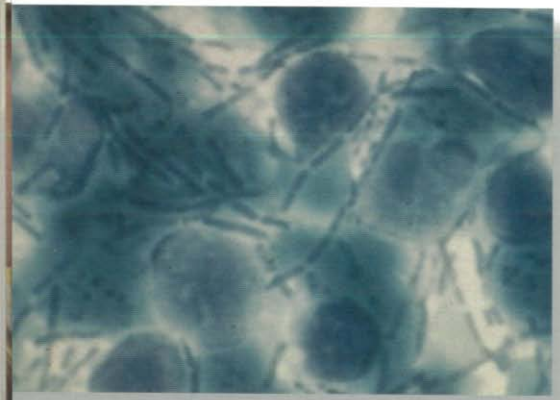
Providing Operational Support

Within 4 months prior to the 2003 Gulf War, BDRD worked with the Chief of Naval Operations to equip the Navy's fleet with full threat agent detection laboratories. First, they trained personnel on board to use the equipment, which includes full confirmatory capabilities. Two ships were tested last summer to see if the labs were effective before they equipped the rest of the fleet. The Afloat laboratories include microbiology capabilities, immunochemical assays, laminar flow hoods, and molecular diagnostics (PCR).

The detection system includes a dry filter unit (DFU) that runs continuously, and is tested twice per day. Rapid detection of any biological threat is especially important aboard ship, so that anyone exposed can be evaluated and treated immediately. BDRD also developed and communicated emergency plans and processes for definitive testing of any potential biological threats.

This is one recent example of how BDRD supports the Navy and Marine forces. They also provide extensive training for forward forces, Naval Environmental Preventive Medicine Units (NEPMU), Marine Chemical Biological Immediate Response Force (CBIRF) and shipboard laboratory technicians operating the Afloat laboratories.

RAPID DETECTION OF ANY BIOLOGICAL THREAT IS ESPECIALLY IMPORTANT ABOARD SHIP, SO THAT ANYONE EXPOSED CAN BE EVALUATED AND TREATED IMMEDIATELY.



DNA-based Vaccine Against Anthrax

BDRD researchers, in collaboration with colleagues at Ohio State University, have expanded their focus to encompass developing a new generation vaccine to improve immunization against anthrax.

The new DNA-based vaccine may require only two shots and be effective against anthrax in just six weeks, thereby fully immunizing the patient in a fraction of the time. If successful, this would simplify the vaccination process of military personnel, who are often moved during the 18 month span the current vaccine requires. DNA formulations may also offer advantages in handling and storage, which are important considerations for stockpiling.

In collaboration with Ohio State University and Vical Inc., researchers identified key anthrax immunogens and verified they can be delivered by formulated DNA. They found by combining two immunogens, Protective Antigen (PA) and Lethal Factor (LA), they may provide broader protection than the currently licenses anthrax vaccine or a single recombinant protein vaccine. A safety and immunogenicity study of this DNA vaccine in humans is expected to begin in late 2003.

This program protects the health and welfare of the military population and helps ensure the success of military operations. In addition, it advances our knowledge of these agents and the diseases they cause, thereby improving measures to protect public health.

The current anthrax vaccine requires a series of six shots and 18 months for the patient to become fully immunized.

National Testing and Analysis

BDRD serves as a national resource, providing testing and analysis for the presence of anthrax and other potential biological hazards. It's portable laboratory, the only one of its kind devoted to detecting biological agents, was deployed to conduct tests at the Pentagon following the crash of American Airlines flight 77 on September 11, 2001, and deployed to New York City to assist with biodetection.

After the subsequent anthrax attacks in October 2001, BDRD analyzed more than 16,000 samples from the Capitol. They detected the presence of anthrax at the Hart Senate Office Building, the Supreme Court, and several area mail processing facilities. The laboratory was also present at the Winter Olympics in Salt Lake City in 2002, available to analyze samples to ensure safety at the games.

THE NEW DNA-BASED VACCINE MAY REQUIRE ONLY TWO SHOTS AND BE EFFECTIVE AGAINST ANTHRAX IN JUST SIX WEEKS, THEREBY FULLY IMMUNIZING THE PATIENT IN A FRACTION OF THE TIME.

Infectious Diseases

MALARIA

U.S. military forces are at great risk of developing malaria while deployed in endemic areas. In fact, more person-days were lost among U.S. military personnel due to malaria than to bullets during every military campaign fought in malaria-endemic regions during the 20th century. To address this threat, researchers with the Military Infectious Diseases Research Program have been investigating methods to control and conquer malaria for more than two decades. This comprehensive research program is at the forefront of malaria research worldwide.

Malaria is a complex parasite, some 300 times more complex than the viruses that most Americans are immunized against. The malaria parasite requires a host to live. As a result, the parasite has evolved with us, and people have evolved to live with the parasite. Additionally, the malaria life cycle is a complex one, unlike most viruses and bacteria.

In order to overcome these obstacles, researchers at the Naval Medical Research Center realized the need for an innovative approach if we are ever to overcome this health threat. They played a key role in the Malaria Genome Project, a consortium that recently determined the entire genetic sequence of the human malaria parasite, *P. falciparum*. They plan to use this data to develop a DNA-based vaccine that will simultaneously attack multiple stages of the parasite's life cycle.

MALARIA

Scientists have been working on malaria vaccines for more than 30 years, with little success. Recently a vaccine called RTS,S developed by GlaxoSmtihKlein and the U.S. Army has shown short term protection. With such a complex parasite, the challenge is daunting.

However, there are two models that suggest that protection is possible. At NMRC, researchers showed that if they bombard *Plasmodium* infected mosquitoes with gamma irradiation, the parasites living inside the mosquito become weakened but not killed. When the mosquitoes are allowed to feed, the "irradiated sporozoites" invade liver cells but do not divide or develop further. This "irradiated sporozoite vaccine" involves allowing 150-200 mosquitoes to feed on the arm of an individual once a month for six months. This provides nearly complete protection against infection with malaria for at least 9 months. While showing protection is possible, a vaccine which requires active biting mosquitoes is of course impractical.

Another vaccine model involves "naturally acquired" immunity. Children raised in malaria endemic areas are continuously exposed to infected mosquitoes, and if they survive to the age of about ten years old they generally develop immunity to malaria. In many parts of the world, nearly all adolescents and adults have malaria parasites in their blood, yet they remain generally free of malaria.

Using these two models of protection, Navy researchers have developed several strategies for vaccine development. To make an effective malaria vaccine, researchers chose proteins that are expressed at key stages of the parasite development. This increases the likelihood that a vaccine composed of such proteins will be effective at preventing both infection and illness in those immunized.

Currently, researchers are testing in clinical trials a vaccine that combines four different DNA-based vaccines either singly or in combination against 5 different parts, or antigens, of the malaria parasite. Three of the candidate antigens are expressed in the liver, where the researchers would like to halt the parasite. In case some parasites make it into the blood stream, there are an additional two antigens, for which the vaccine would target the parasite at this stage of the disease.

NMRC's Malaria Program conducted the first-ever clinical trial in healthy humans using a multigene DNA-based vaccine. Though not designed to be protective, this vaccine was shown to be safe, well tolerated and produced cellular immunity against the parasite antigens. Researchers are now focusing on a series of clinical trials of a 2nd generation vaccine in the U.S. that will test the efficacy of vaccines in volunteers who have agreed to be infected with the malaria parasite, using a strain easily treated by drugs. The results of vaccine studies in overseas locations such as Ghana, West Africa, will be particularly significant to this research because it is important to test vaccines under conditions where the parasite lives and infects people.

NMRC researchers are also developing novel technologies to exploit the vast amount of data generated from the genome project for use in drug and vaccine development. For example, the NMRC team produced the first chromosome-specific DNA microarray, which enables research on the expression of thousands of genes simultaneously. They also helped develop a relational database to handle the data, and pioneered a partnership with Scripps Research Institute to develop a high-throughput proteomics method to identify thousands of malaria proteins throughout the parasite life cycle. They have also recently established the Malaria Functional Genomics Consortium which brings together a diverse group of experts from various disciplines to fully realize the potential of the completed Malaria Genome.

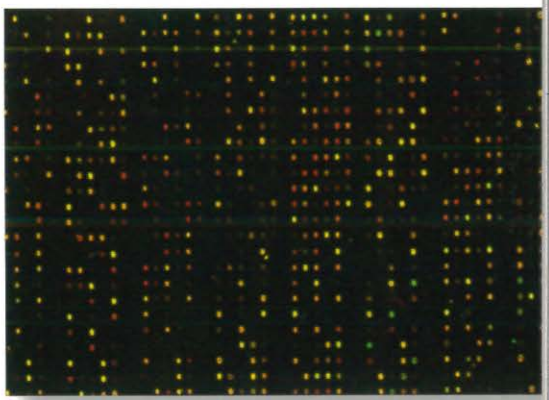
These partnerships and new technologies, along with information from the genomic project, should lead to better understanding of the malaria parasite and its interactions with its host, and move us closer to a viable vaccine and more effective drugs.

Malaria Genome Project

In 2002, the applied genomics arm of the NMRC Malaria Program worked with an international consortium to determine the entire genetic sequence of the human malaria parasite, *P. falciparum*.

The sequencing data provides new insights that researchers need to develop effective vaccines, control strategies, and treatments for this complex disease.

This project, envisioned by leaders of the NMRC's Malaria Program, began in 1996 and included The Institute for Genomic Research (TIGR), the Sanger Center, and Stanford University, with funding from the DoD, NIH, Burroughs Wellcome Fund, and the Wellcome Trust. NMRC researchers helped identify capabilities and requirements for the project, and helped ensure success of the team.



THIS GENETIC BLUEPRINT WILL PROVIDE THE SEQUENCE OF EVERY POTENTIAL VACCINE AND DRUG TARGET AND WILL LIGHT THE WAY TOWARDS MALARIA RESEARCH INTO THE 21ST CENTURY.

DENGUE

More than 2.5 billion people, that's more than a third of the world's population, live in dengue fever endemic areas. The global prevalence of dengue fever has grown dramatically in recent decades. There are a staggering 100 million infections each year that range from a simple viral infection that people recover from in a few days, to dengue hemorrhagic fever, a painful form of the disease that can be fatal.

The disease is transmitted by an "urban" mosquito called *Aedes aegypti*– which spreads the debilitating arbovirus infection. Experts call this mosquito urban because it has adapted to living in populated areas, frequently using man-made containers that hold water for laying eggs and feeding on people inside houses.

Dengue fever has had a negative impact on military operations dating back as far as World War II. In recent military operations in Somalia and Haiti, dengue fever was a leading cause of illness among hospitalized soldiers.

There are four closely related, but antigenically distinct, virus serotypes. If a vaccine does not provide thorough protection against all of these, then re-infection with a virus serotype against which there is no or only partial immunity could lead to a hemorrhagic form of this disease.

NMRC researchers began to pursue the development of a DNA vaccine for dengue fever because attempts by military researchers over the last 50 years have met with limited success. Because no live viruses are involved, the DNA route has the potential to result in a vaccine that does not run the risk of producing dengue-like symptoms like the live attenuated vaccines. At the same time, DNA vaccines are able to give precise instructions to the body so that it will make different immune responses for different strains of the same disease at once. Early studies show that a DNA vaccine targeting dengue-1 elicits a protective immune response in animals. This approach involves the use of naked DNA in the form of a circular DNA molecule known as a plasmid vector. Work in mice demonstrated that long-lived anti-dengue neutralizing antibody could be produced using the DNA vaccine approach.

Early studies showed that the vaccine can offer protection in a live virus challenge model. These studies, along with many others, help show that the DNA vaccine approach is a viable one. Scientists plan to begin human Phase I clinical trials in 2003. Dengue researchers at NMRC are also developing a DNA vaccine using Molecular Breeding™ (DNA shuffling) technology, through a collaboration with Maxygen, Inc. They hope to use this new technology to produce a single DNA vaccine construct capable of generating tetravalent anti-dengue neutralizing antibodies.

Working in collaboration with other scientists, researchers at NMRC were the first to show that dengue viruses infect and replicate in human dendritic cells, a cell type that plays a critical role in the body's immmue response to pathogens. This discovery is leading to new insights on how to develop an effective vaccine to protect against dengue.

Another important area of research for the military is in diagnostics. The symptoms for dengue fever are similar to that of typhoid and malaria, so clinicians need a tool to quickly ascertain if the fever is caused by dengue. Researchers at NMRC are developing and validating methods for accurate diagnosis in deployed military personnel. Several assays developed by private industry have been evaluated by NMRC and at the Naval Medical Research Unit #2 (NAMRU-2) in Jakarta, Indonesia, where they were shown to be reliable.

To gain more insight into this disease, researchers at NAMRU-2 conducted a prospective study of dengue fever (DF) and dengue hemorrhagic fever in a cohort of 2,400 children. To better define the pathophysiology of dengue in adults, a prospective study of DF and DHF in young adults is ongoing in Bandung, West Java, Indonesia.

Data generated from these studies will provide better understanding of the immunological requirements for protection against these diseases. Studies conducted at the Naval Medical Research Center Detachment in Peru also have contributed to our understanding of dengue fever and DHF by showing that genetic variation of the dengue virus genome may play an important role in disease outcome.

THE DISEASE OFTEN ESCALATES INTO EPIDEMICS VERY QUICKLY BECAUSE IT IS ENDEMIC TO AREAS AND SITUATIONS THAT HAVE PEOPLE LIVING IN CLOSE QUARTERS.

SCRUB TYPHUS

Since World War II, researchers at NMRC and at WRAIR have studied Rickettsial Diseases and how to minimize their impact on military operations and international public health.

Rickettsiae are a diverse collection of bacteria. Because they are obligate intracellular parasites, they can live only within the cells of other animals. A general characteristic of rickettsiae is that arthropods play an essential role in their life as either the natural host or as a vector to other hosts such as various species of birds and mammals (including humans).

Camp Fuji in Japan has had a sporadic history of scrub typhus outbreaks, occurring as early as 1948. In 2000 and 2001, there were outbreaks of a febrile disease among U.S. Marines training there. Serum samples from both outbreaks collected by NEPMU-6 were flown to NMRC, where the Rickettsial Disease Department laboratory confirmed that the disease was scrub typhus.

Rickettsial diseases have had a significant impact on military operations throughout history. One disease with particular military importance is scrub typhus, a febrile illness with mortality rates as high as 50% in untreated patients. It is a major concern today for troops deployed to endemic regions of Asia, Australia, and the Western Pacific. Antibiotic-resistant strains are also emerging in areas where U.S. troops may be deployed, and where they currently conduct training and provide humanitarian assistance

Scrub typhus is an infectious disease that is transmitted to humans through the bite of infected mites that live on field mice and rats. The main signs and symptoms of the disease are fever, headache, a wound around the bite (eschar), a rash on the trunk, and swelling of the lymph glands. Accurate diagnosis is very important, because without appropriate antibiotic treatment it can be fatal. Differentiating scrub typhus from other diseases is often difficult during the first several days before the initial rash appears.

NMRC researchers have worked to develop new rapid diagnostic assays that allow clinicians to accurately detect this disease. They recently identified a recombinant outer membrane protein (Karp r56), which is used in a commercial rapid diagnostic assay for scrub typhus. In addition, NMRC researchers have developed a real time polymerase chain reaction (PCR) assay for scrub typhus that is very sensitive and specific. Since scrub typhus is included on the biological select threat agent list, these technologies will enable the military to rapidly detect deployed bio-terrorism agents to which troops may be exposed.

The development of a safe, effective vaccine for scrub typhus is a priority to reduce the risk to our exposed military personnel and civilians who are susceptible to the disease. NMRC researchers are developing a multivalent vaccine, utilizing recombinant proteins and naked DNA, that will provide long-term protection for military personnel.

In addition to their work on scrub typhus, NMRC researchers are developing real-time PCR assays for epidemic typhus, Rocky Mountain spotted fever, and ehrlichial, bartonella and borrelial diseases of military importance. They also conduct epidemiologic studies, in conjunction with the DoD overseas labs, to determine the risk posed by rickettsial diseases and other arthorpod borne diseases such as Lyme disease, and to identify etrologic agents in current outbreaks.

ENTERIC DISEASES

Throughout history, diarrheal diseases have had a major impact on military operations, and led to a significant loss of man-days on the battlefield. On Navy ships, this type of illness can be especially devastating. In addition to the direct impact on the fighting forces, there is an indirect impact on the medical staff, logistics for treatment, and increase needs for supplies and waste disposal.

Enteric researchers work in close collaboration with their colleagues at Walter Reed Army Institute of Research (WRAIR) and with researchers at the DoD overseas laboratories, to identify enteric health threats, define the most effective treatment options, and develop and test new preventive measures.

Today, when significant diarrheal illness develops, military medical providers use the most effective treatment including antibiotics, antimotility agents when appropriate, and fluid therapy to limit the impact on troops. But as antibiotic resistance patterns change, new medicines become available, and regional pathogen differences are identified, NMRC researchers work to define the best treatment regimens. Recent studies have shown that azithromycin is the most effective treatment for travelers' diarrhea in Thailand where *Campylobacter* is a common cause, and are now testing this regimen in other regions.

Providing the best treatment, along with intense preventive medicine efforts, is important but not nearly enough to overcome this health threat. Because of the great impact these diseases can have on troops, NMRC researchers are actively pursuing vaccines for enterotoxigenic E. coli, and *Campylobacter jejuni*, two of the most common causes of diarrhea in deployed forces.

Navy researchers have a long history of contributions to enteric diseases research. During World War II, Navy Lieutenant Robert Allen Phillips developed a field method to rapidly assess fluid loss in wounded servicemen. This innovation, along with additional research by Philips and others, led to the development of effective intravenous and oral rehydration therapy for the treatment of cholera and related diarrheal illnesses. These simple treatments are used everyday by parents and healthcare workers around the world, saving millions of lives annually. Phillips was instrumental in establishing the United States Naval Medical Research Unit No. 3 in Cairo, Egypt in 1946, and the United States Naval Medical Research Unit No. 2 in Taipei, Taiwan in 1955. He also served at the helm of both units.

ENTERIC DISEASES

Enterotoxigenic *E. coli*

Most *Escherichia coli (E. coli)* are normal inhabitants of our environment and gastrointestinal (GI) tracts and do not cause disease. However a number of different, so called diarrheagenic E. coli have the ability to colonize the GI tract and cause diarrhea in humans and animals. The most common is *enterotoxigenic E. coli* (ETEC), the most important cause of travelers' diarrhea in U.S. forces deployed to less developed countries and the leading cause of bacterial diarrhea in children living in these less developed regions of the world. In fact, in developing countries a quarter of all disease in children under the age of three is caused by this strain of bacteria. ETEC cause disease by attaching to the intestinal lining through specialized projections called fimbriae. Once attached, ETEC multiply and produce toxins that stimulate an outpouring of intestinal fluids, which can cause diarrhea and consequent dehydration. Researchers at NMRC are developing vaccines that would block attachment, and toxin activity, interrupting the infection at its earliest stages, which should reduce the number and severity of ETEC diarrhea cases.

A killed, whole cell ETEC vaccine developed by researchers in Sweden, showed a great deal of promise and has been tested extensively by Navy researchers in Egypt. The vaccine underwent extensive safety testing in Swedish, U.S. and Egyptian adults. After IRB approvals in the United States and Egypt, and review by an independent safety board, it was tested for efficacy in Egyptian children. Because of the high disease burden in Egyptian children, efficacy testing was logistically feasible, and if the vaccine were effective they would benefit from a newly approved vaccine. In addition, a young child's naive immune system resembles that of a military or civilian traveler going to a developing country, so the studies would support licensure in children and adults. While the vaccine used in that study was proven not effective, the information from the trial has helped researchers progress incrementally in their quest to overcome this important health threat.

NMRC researchers are now focusing on purified versions of the whole fimbriae, as well as a more refined approach using just the "gripping" or binding portion of the fimbriae. Either of these could be used to make a subunit vaccine that incites the body to produce adherence-blocking antibodies. The theory is that the binding portion, which sits at the tip of the fimbrial structure would make a much more potent vaccine. Methods are being developed in the laboratory to make a stable version of these tip proteins. Results are promising, and should lead to clinical testing within a few years.

ENTERIC DISEASES

The strains of Campylobacter found in Thailand are almost all resistant to the antibiotics used most often to treat travelers diarrhea. NMRC researchers have been working with an Army Laboratory, the Armed Forces Research Institute of Medical Sciences (AFRIMS), to study these strains of the disease and the drug resistance. Since prevalence is so high here, this will likely be the site of future clinical studies on any Campylobacter candidate vaccines.

Campylobacter jejuni

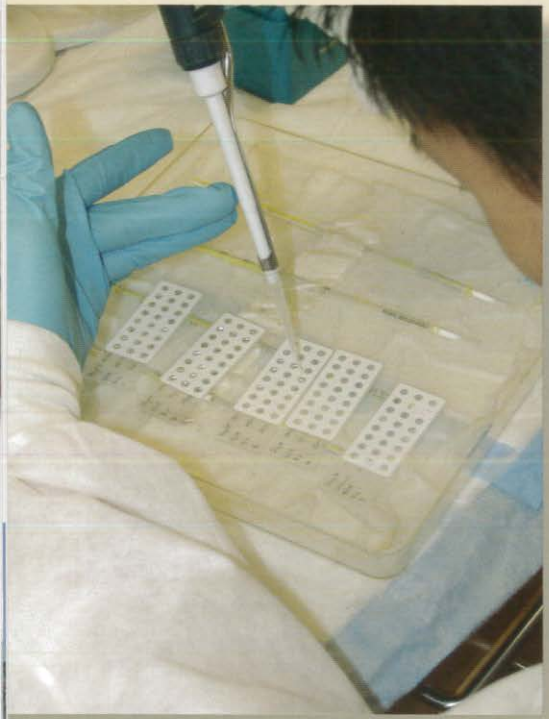
Campylobacter jejuni is a relatively newly identified pathogen, yet it has been a focus of the Navy enterics research program since its importance was first recognized. A food-borne pathogen, *Campylobacter jejuni* is the most common bacteria cause of diarrhea in the U.S. and probably the second most common cause of travelers' diarrhea worldwide. This problem is further complicated because over time, some strains of this bacterium have become drug resistant.

Campylobacter jejuni causes a more severe disease than ETEC, causing high fever, severe stomach cramps, headache and joint pains in addition to diarrhea. For troops this means a more prolonged, temporarily debilitating illness with a significant impact on military readiness. Some cases of *Campylobacter* diarrhea can be followed by a much more serious autoimmune disorder called Guillian-Barré Syndrome (GBS). GBS is characterized by paralysis beginning in the legs and moving up the body, sometime causing paralysis of the respiratory muscles.

The program at NMRC has always focused on vaccine development, but a great deal of basic work first had to go into understanding how the organism caused disease, and what kind of an immune response protected people against a second infection. The Enteric Diseases Department at NMRC has been a world leader in this field. They have identified many surface structures of the bacteria, found how it invades human cells, and characterized many aspects of the immune response. This work continues with the use of comparative genomics, expression arrays, and studies to try and better understand the protective immune response. All of which will enable researchers to develop an effective vaccine. Their task is complicated by the fact that there are many different strains, or serotypes, of *Campylobacter* the world over. Therefore, the researchers must find common antigens across *Campylobacter* strains or antigens specific to certain disease types, which can be used to make a vaccine that will work on the most prevalent serotypes. Researchers at NMRC are also studying the biosynthesis of ganglioside-like structures involved in causing GBS and in disease protection, trying to understand their role in pathogenesis, which could lead to the development of further vaccines.

The two current vaccine candidates are a killed whole cell vaccine, and recombinant protein vaccine. The killed whole cell vaccine is the only *Campylobacter* vaccine ever tested in volunteers. Given as a drink, the vaccine is safe, and the NMRC team has found a way to deliver it that produces significant intestinal immunity. This vaccine is continuing to move forward to efficacy trials. As an alternative strategy, the NMRC team is also developing a recombinant protein vaccine. Beginning with a recombinant flagellin protein, the plan is to add additional protective antigens in a multi-antigen final vaccine.

AGILE VACCINE PROGRAM



Continued vaccine development is imperative for the health of everyone, especially military personnel who are deployed worldwide. Troops are at risk of contracting highly debilitating and life-threatening illnesses when they are sent to countries with high incidence of infectious diseases. In addition, vaccines and immunization are extremely cost-effective health interventions. These factors make it vital that vaccines are developed quickly and efficiently to protect people at risk.

US military medical researchers have a long history of success in vaccine development for a wide variety of diseases. The technology associated with most of the vaccines in use today has changed very little since Edward Jenner first inoculated an eight-year-old in 1796. Some of the disease threats today are more complex.

In recent years, advances in DNA research have enabled scientists to begin working with a DNA-based vaccine model. This technology holds great promise in combating bio-terrorism, emerging, and genetically-modified threats—areas especially important to protect U.S. military personnel. This technology may enable researchers to rapidly produce and alter new vaccines and potentially combine many vaccines (multivalent).

DNA-based vaccines are relatively simple to produce, alter, manufacture, and purify, and are fundamentally different from the vaccines in use today. Rather than immunizing with foreign material (either the killed or weakened infectious agent, or a portion of it), DNA-based vaccines immunize with the genetic blueprint of that foreign protein. The body's own cellular machinery uses this genetic blueprint to produce the foreign material that is then recognized by the human immune system. DNA-based vaccines have the ability to induce both antibodies (humoral) and cellular immunity, which is important to be able to respond to a variety of organisms. After vaccination, if a live organism enters the body, the immune system will rapidly respond to eliminate the infection

NMRC researchers quickly saw the advantages of DNA-based vaccines, and have been at the forefront of developing these types of vaccines for several diseases including malaria, dengue fever, and anthrax. In fact, they were among the first to administer DNA-based vaccines to healthy humans, as part of a clinical trial for a DNA-based malaria vaccine.

In 2002, NMRC established an Agile Vaccine Program, which promises to expand our knowledge of this powerful new technology. It seeks to develop a broad-based platform for developing and administering DNA-based vaccines. NMRC researchers are currently studying this technology and its potential to protect against a parasite: malaria; a virus: dengue fever; and a bacterium: anthrax. Both anthrax and dengue fever are potential bio-warfare threats.

This program fosters collaboration among scientists studying different diseases, and will help move this technology closer to a reality. NMRC scientists leverage their resources and talents by working closely with universities, private industry and other government agencies. These private-public partnerships maximize respective technologies, capabilities, and infrastructure.

DNA-based vaccines could provide a huge leap forward in modern medicine. NMRC researchers are committed to developing a platform that could, once proven effective, be used to help combat a wide variety of diseases to protect our armed forces and save lives around the globe.

GLOBAL EMERGING INFECTIONS SYSTEM (DoD-GEIS)

The range of infectious disease threats is rapidly changing, along with dramatic changes in society and the environment. Despite predictions to the contrary, people today remain susceptible to a variety of new and resurgent diseases.

Both naturally occurring and bioterrorist infectious disease agents have an increasing potential to destabalize international security. U.S. military personnel have a higher risk of exposure to emerging infections occurring both naturally and from bioterrorism. The fact that infectious disease spread rapidly around the globe today, as evidenced in the 2003 SARS outbreak, makes world-wide surveillance for emerging infections vital.

The DoD-GEIS was established in response to a 1996 Presidential Decision Directive, which expanded the mission of the DoD to include support of global surveillance, training, research, and response to emerging infectious disease threats.

U.S. MILITARY PERSONNEL HAVE A HIGHER RISK OF EXPOSURE TO EMERGING INFECTIONS OCCURRING BOTH NATURALLY AND FROM BIOTERRORISM.

The three Navy and two Army overseas infectious disease research laboratories provide a unique network of state-of-the-art facilities to carry out the mission of DoD-GEIS. The five laboratories, referred to as Outside the Continental United States (OCONUS) laboratories, provide unique research platforms and operate over three continents: Africa (NAMRU-3 in Egypt, USAMRU-K in Kenya), Asia (AFRIMS in Thailand, NAMRU-2 in Indonesia), and South America (NMRCD in Peru).

These laboratories help the GEIS carry out its goals of surveillance for action, response, and host-nation training and capacity building. The central surveillance focus is on drug-resistant malaria, drug-resistant enteric organisms, unexplained febrile illnesses, and influenza.

The program's strategy reflects a comprehensive interagency systems approach, working in concert with other federal, private, and international organizations. This helps strengthen the worldwide effort to combat this global issue. The DoD laboratories work extensively with local health officials, and leverage their host region capacity through laboratory and epidemiology training. Highlighted here are some major contributions that the Navy overseas labs provide to this global effort.

Naval Medical Research Unit No. 2 (NAMRU-2) Jakarta, Indonesia

NAMRU-2 is a World Health Organization (WHO) Collaborating Center for New and Re-emerging Diseases, and is actively involved in the development of regional outbreak recognition and response capabilities.

Outbreak Response Training Workshops conducted by NAMRU-2 staff throughout Southeast Asia help build regional public health capacity. NAMRU-2 also supports regional capabilities by transferring diagnostic testing capabilities to host-nation lab facilities.

NAMRU-2 GEIS has successfully implemented and expanded two internationally recognized model programs for establishing a global disease surveillance and response system, based on regional hubs and linked by modern communications.

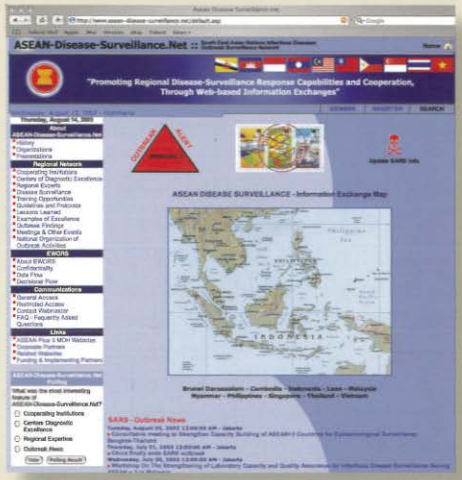
The first, the Early Warning Outbreak Recognition System (EWORS), is a software-driven surveillance tool that enables operators to input and analyze the signs and symptoms of patients reporting to medical treatment facilities with suspected infectious diseases. It can help detect rises of clustered signs and symptoms suggestive of outbreak occurrence.

EWORS, developed at NAMRU-2 in Jakarta in collaboration with the Indonesian Ministry of Health, is currently being used by the public health sectors of Indonesia, Cambodia, Vietnam, and Lao PDR. The technology recently secured preliminary patent approval in the United States.

ASEAN-Disease-Surveillance.Net, the Association of Southeast Asian Nations (ASEAN) web-based outbreak response network, was developed by NAMRU-2 and the Indonesian Ministry of Health. It is used by 10 countries to report and track infectious disease outbreaks between countries and with the WHO Regional Offices.

NAMRU-2 GEIS surveillance activities have led to many important contributions including:

- Recognition of leptospirosis as a significant cause of febrile disease in Indonesia, Cambodia, Laos, and Vietnam
- Decline in incidence of Vibrio cholerae, the rise of Shigella flexneri, and the re-emergence of Shigella dysenteriae after a 15-year absence in Indonesia
- First-ever finding in the world of chloroquine resistance to Plasmodium malariae in South Sumatra and the re-emergence of malaria in a coastal tourist area close to the megatropolis of Jakarta after an absence of disease for over 25 years



GLOBAL EMERGING INFECTIONS SYSTEM (DoD-GEIS)

U.S. Naval Medical Research Unit No. 3 (NAMRU-3) Cairo, Egypt

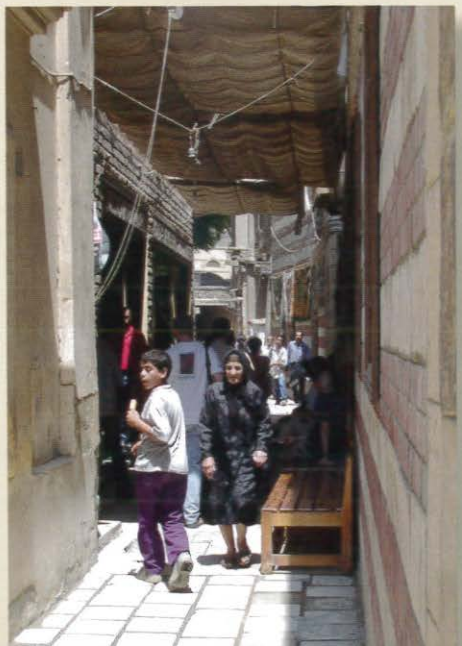
NAMRU-3 has established an impressive GEIS program that focuses on supporting infectious disease operational research and surveillance in Egypt and throughout the western Mediterranean region.

Their GEIS program is an integrated effort through well-established partnerships with other agencies in the area including USAID, Department of State, the Centers for Disease Control, and the Egyptian Ministry of Health and Population. Navy scientists helped develop the Egyptian National Guidelines for Communicable Disease Surveillance, along with a solid quality assurance laboratory assessment and training program.

They have also conducted surveillance training throughout the region in over 12 countries in Africa, the Middle East, and Central Asia, including 14 governorates and 137 districts. The training provided by NAMRU-3 includes basic epidemiology, computer technology, statistics, surveillance, and outbreak investigations. After receiving training, participants then form Epidemiology Surveillance Units (ESU), which report on the incidence of "reportable prioritized diseases."

NAMRU-3 scientists have begun to work in Central Asia to conduct GEIS surveillance for influenza and Crimean-Congo Hemorrhagic Fever (CCHF) in Kazakhstan; CCHF, meningitis and acute febrile illnesses in Uzbekistan; and hemorrhagic fever and encephalitic viruses in the Crimea and Western Ukraine. These efforts are critical to developing a more clear understanding of emerging infections in this important region. NAMRU-3's extensive surveillance activities have resulted in many notable achievements:

- Documented Haemophilus influenzae serotype b (Hib) as the major cause of childhood meningitis and the emergence of brucellosis (previously misdiagnosed as Salmonella typhi - typhoid fever) as a cause of acute fever in Egypt
- Identified and mapped areas of risk for Rift Valley Fever (RVF) in Saudi Arabia prior to a joint exercise between the U.S. and Saudi Arabian militaries
- Rapidly responded to several infectious disease outbreaks including RVF in Yemen and Saudi Arabia, waterborne salmonellosis in the Nile Delta, and newborn sepsis in a hospital in Egypt.



Naval Medical Research Center Detachment (NMRCD), Peru

In South America, the incidence of influenza is poorly understood because surveillance is either lacking or relies entirely on clinical diagnoses unsupported by diagnostic laboratory testing. The critically needed data to develop and target vaccines are not available. These enormous gaps in the surveillance system in South America may enable strains to emerge for which vaccines cannot be prepared in time to abort a pandemic.

NMRCD has established strong collaborations with public health personnel at all levels throughout South America, and contributes to the WHO regional influenza surveillance network. They hope to establish and integrate a functional influenza and ARD surveillance program into existing national disease surveillance systems. The results will be used to develop and target vaccines for the prevention of influenza and other ARD agents.

Malaria is another important health issue in the region. NMRCD staff has made significant contributions to local knowledge about malarial drug resistance in Peru and other countries which make up the Amazon Basin. NMRCD staff has found varying levels of widespread resistance of *Plasmodium falciparum* to chloroquine (CQ), sulfadoxine/pyrimethamine (SP), and/or mefloquine (MQ). Based on these and other studies, Peru became the first country in South America to recommend SP-artesunate combination therapy that varies by region. Training for Bolivia's malaria control staff to conduct in-vivo anti-malarial resistance studies led to changes in the country's anti-malarial therapeutic recommendations.

Mosquito surveillance in the Amazon Basin region of Iquitos, Peru, has been an active and crucial GEIS activity to document emerging arboviral threats and appropriate control measures. When surveillance began in 1996, only 25 species of mosquitoes were known in this region. By the beginning of 2002, over 100 species had been catalogued by the Smithsonian Institution in Washington, DC. Viral isolates identified with support by USAMRIID and the University of Texas, Galveston, have yielded over 16 different viruses including Eastern Equine Encephalitis. Comparing mosquito viral patterns and human sera is yielding a more accurate picture of arboviral threats in the region.

Finally, NMRCD has been a leader in surveillance for antibiotic resistant enteric organisms in Peru and Bolivia. Continued multi-drug resistance in Shigella, increasing Ciprofloxacin resistance in Campylobacter, and emerging multi-drug resistance of Salmonella and Escherichia coli have been documented. NMRCD and the Bolivian Technologic Food Institute in Sucre, Bolivia, co-sponsored a landmark drug resistance symposium highlighting these enteric resistance patterns bringing to the forefront the attention needed to act responsibly to make future changes.

THESE ENORMOUS GAPS IN THE SURVEILLANCE SYSTEM IN SOUTH AMERICA MAY ENABLE STRAINS TO EMERGE FOR WHICH VACCINES CANNOT BE PREPARED IN TIME TO ABORT A PANDEMIC.

Combat Casualty Care

COMBAT INJURY AND RADIATION REPAIR PROGRAM

Military personnel are at significant risk of dying from massive tissue loss in combat operations. A blast, thermal burn, or radiation burn can result in long-term physical disability or psychological trauma for those service members who do survive. Present day surgical techniques, which involve partial thickness skin grafts (muscle or bone) from unburned areas of the same individual, are inadequate to repair large tissue injuries because there is a limited amount of donor skin (muscle or bone) available.

Investigators at the Combat Injury and Radiation Repair Program (CIRRP) are examining ways to improve cell regeneration and diminish immune rejection in tissue repair. If successful, the research findings will not only address combat casualty needs, but also benefit the civilian medical community.

COMBAT INJURY AND RADIATION REPAIR PROGRAM

The development of strategies that can induce tolerance to the transplanted organ would be of significant use to military personnel. The study of the immune system suggests that there may be alternative strategies that would improve the body's ability to accept foreign tissue.

The Navy's research is further enhanced by a collaboration with the University of Maryland, a leader in organ transplantation and in the care of patients with traumatic injuries. This partnership allows NMRC to leverage its scientific expertise with other investigators with separate funding. The academic medical center is also equipped to perform clinical trials of developed technologies in its Shock Trauma Center, as well as Organ Transplantation Division, in adapting those technologies for military use.

At the core of CIRRP research efforts is the study of the use of expanded stem cells, derived from bone marrow, to facilitate recovery of lost marrow from radiation and chemical weapon exposure (e.g. mustard gas). One strategy, currently in pre-clinical studies, is to expand the patient's own residual stem cells after radiation. Navy scientists have developed two culture systems that support the growth and "expansion" of bone marrow cells in ex-vivo culture. After 7-10 days of culture with endothelial cell lines, the number of bone marrow stem cells, as well as more mature bone marrow progenitor cells, can be expanded four to twenty-fold.

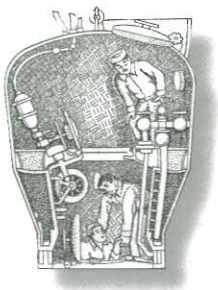
Parallel investigations are looking at the use of expansion technology to increase the number of stem cells in umbilical cord blood. Human umbilical cords are a rich source of blood-forming stem cells, but low cell numbers limits their use in adult patients who require stem cell transplantation. Current research is looking at methods of cord blood expansion in order to increase the number of immature stem cells present to hasten blood count recovery. Significant strides would be achieved if the cell number could be expanded three to five-fold.

Cord blood transplants could prove more effective than bone marrow transplants in the treatment of radiation injuries. Cord blood cells are already tissue-typed and stored and therefore could be infused within one week of a request. They also are more "forgiving," allowing for greater tissue-type (HLA) disparity. And they can be obtained non-invasively from umbilical cords that would otherwise be discarded.

BONE MARROW INJURY IS A MAJOR CAUSE OF DEATH AFTER JUST MODERATE EXPOSURE TO RADIATION—A SERIOUS RISK FOR MILITARY PERSONNEL—AND CURRENT THERAPIES HAVE PROVEN INEFFECTIVE OR TOXIC.

UNDERSEA MEDICINE

USS Squalus (SS-192), a diesel-electric submarine built at the Portsmouth Navy Yard, Portsmouth, New Hampshire and commissioned there on March 1, 1939, suffered a catastrophic valve failure during a test dive off the Isle of Shoals on May 23. Partially flooded, the submarine sank to the bottom and came to rest keel down in 60 fathoms (240 feet) of water. Navy divers and salvage ships responded quickly, and the following day began operations to rescue the surviving 32 crewmembers and one civilian from the forward sections of the boat.

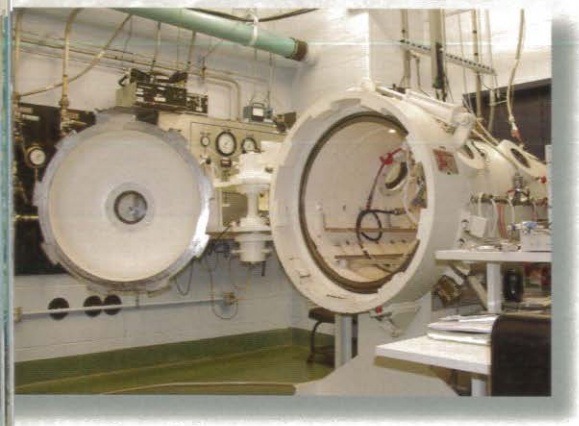


The USS Falcon (ASR-2) lowered the newly developed McCann rescue chamber—a revised version of a diving bell invented by Commander Charles B. Momsen—and, over the next 13 hours, all 33 survivors were rescued from the stricken submarine. Navy doctor Lt. Albert R. Behnke, reporting on the rescue of the survivors wrote, "... it has been possible in the decompression of divers to bring them rapidly to the 50-foot level where they remain breathing oxygen until the excess gas pressure in the body has decreased to the point where immediate surfacing is safe." This seminal event highlighted the Navy's early interest in the medical perils of undersea operations.

More than 60 years later, investigators in NMRC's Operational and Undersea Medicine Department are still searching for ways to further increase the safety and improve the operational capabilities of U.S. Navy SEALS, divers, and submariners. The biomedical problems posed by potential submarine rescue scenarios in the 21st century are among the topics under study.

Crewmembers on a disabled submarine (or divers) who breathe air at high pressure are at risk for developing severe (potentially fatal) decompression sickness (DCS) if brought to the surface too quickly. DCS occurs when biologically inert gas (nitrogen in the case of air-breathing) accumulates in tissues under pressure, then bubbles up (like champagne after the cork is popped) in those tissues when the pressure is released too quickly. Bubbles forming in the blood and/or tissues can cause symptoms ranging from joint pain to paralysis or death. Standard preventive and treatment measures have not changed much since the rescue of the Squalus. Divers adhere to slow/controlled decompression schedules to allow off-gassing while avoiding bubble formation (slowly opening the champagne bottle). Breathing high concentrations of oxygen (and therefore less inert gas) is also used to minimize DCS risk and in the treatment of cases that do occur. These standard preventive and treatment measures require large, heavy, and complicated hyperbaric chamber and gas-plumbing facilities that are expensive and logistically burdensome. They also run the risk of inducing hyperbaric oxygen (HBO) toxicity that can result in convulsions or lung damage if high concentrations of oxygen are breathed under pressure for too long.

UNDERSEA MEDICINE



One of the Holy Grails of undersea medicine research is the development of the ability to prevent and treat DCS without the need for hyperbaric support facilities. In pursuit of that end, investigators at NMRC have demonstrated, in experimental models, that they can reduce the incidence of decompression sickness by 50% by administering compounds that enhance the body's ability to rid itself of inert gas rapidly. Significant research is targeting the use a liquid oxygen-carrying drug called perfluorocarbon (PFC). It not only carries oxygen, but also nitrogen. When combined with plasma, the PFC-plasma mixture carries more oxygen than it otherwise would. By increasing the solubility of plasma for nitrogen, researchers hypothesize the same conditions will apply and the body will carry more nitrogen. If proven effective, PFC would allow divers to go to deeper depths for longer periods of time and resurface faster, decreasing their risk for decompression sickness. Other investigations are examining the basic biomolecular pathways responsible for DCS.

On a related front, other investigators at NMRC are analyzing the phenomenon of HBO convulsions. One group of studies is searching for non-invasive ways to predict, in individuals, when a hyperbaric oxygen convulsion is about to occur, thereby enabling divers or combat swimmers to avoid their occurrence during a military operation. Another group is searching for explanations for the biomolecular mechanisms whereby hyperbaric oxygen exposure causes nerve cells in the brain to produce convulsions.

By developing newer decompression methods, researchers believe their findings will have far reaching effects, improving the health and safety of both commercial and sport divers as well as military personnel. The careful study of the convulsions associated with HBO is also expected to shed light on the mechanisms involved in epilepsy and other seizures.

The nature of modern day warfare has caused significant changes in the way combat casualty care is delivered to service members on the front lines. In current military operational scenarios there is minimal forward medical support for personnel wounded during battle. Military doctors rely on an ever-growing arsenal of technologically advanced pharmaceuticals and medical devices to treat patients in the field. And in many cases, due to logistics, there exists the possibility of prolonged periods without adequate medical care. This is of particular concern in cases of severe hemorrhage, the leading cause of death in combat.

The Resuscitative Medicine Department at the NMRC is dedicated to the development of new techniques and technologies so that first responders may provide faster initial resuscitation of casualties and safer transportation to locations with adequate medical care.

RESUSCITATIVE MEDICINE

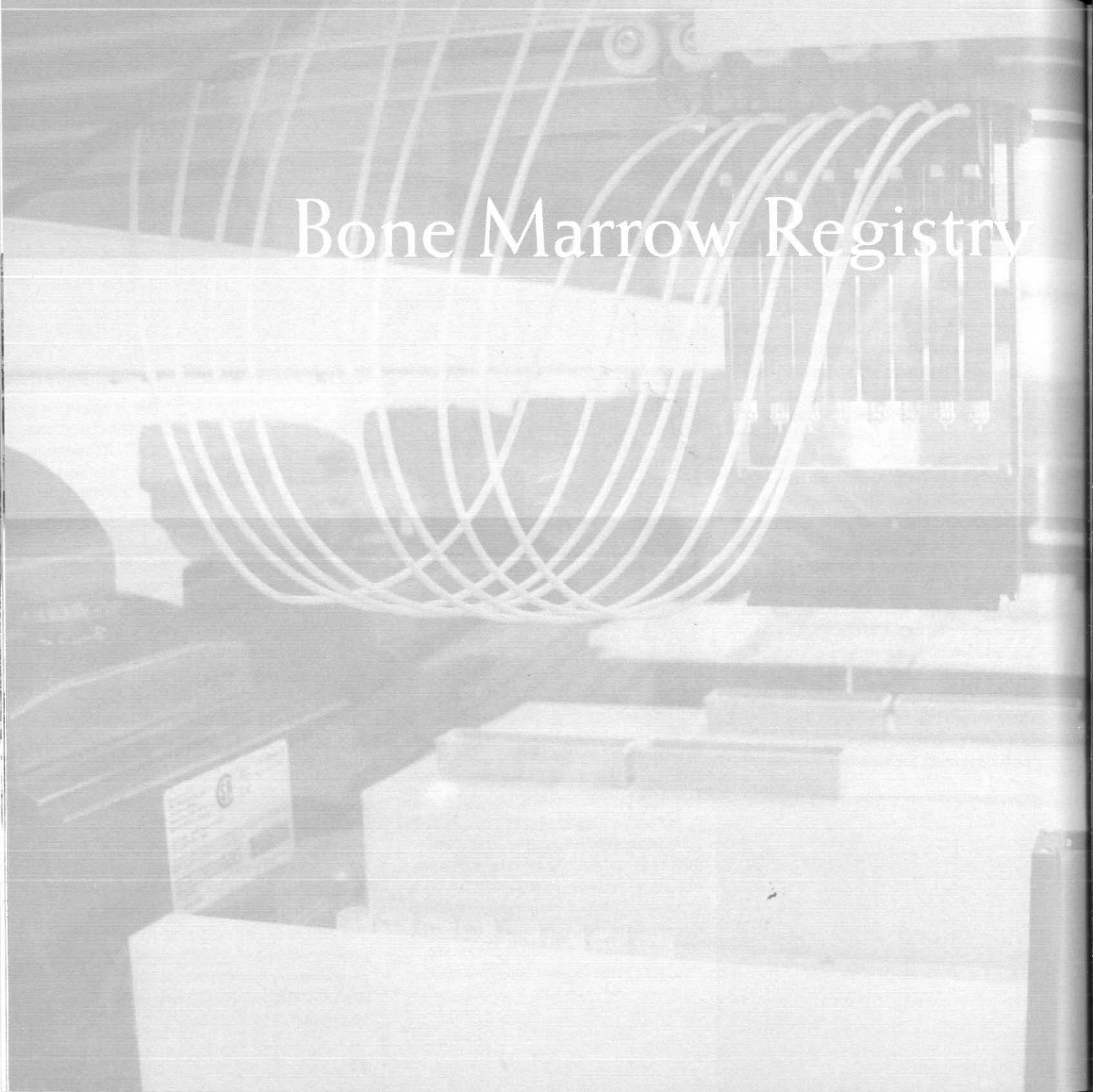
Investigators of the Metabolic Regulation Program are examining a pharmaceutical intervention that can be immediately administered by injection and/or inhalation to combat casualties suffering from severe blood loss (hemorrhage) and traumatic injury. Researchers hope to develop pharmacological treatments to induce tolerance to blood loss and hemorrhagic shock using hibernation-specific factors.

The phenomenon of hibernation is associated with a variety of physiological responses including reduced heart rate, respiration rate, blood flow, and oxygen consumption. These responses are similar to the decreased heart rate, body temperature, and blood pressure observed in combat casualties. Hibernation, along with its associated drop in body temperature, is being studied in an attempt to develop treatments to minimize the effects of hemorrhage and major traumatic injury. Such treatments are based on the regulation of metabolic rate and oxygen requirements and may lead to pharmacological treatments, which involve induction of hypothermia or use of hibernation-specific factors. If some of the physiological responses associated with hibernation could be induced in a casualty, additional time to access required medical care might be achieved allowing lives to be saved.

In related studies, the Hematomimetics Program is looking at alternatives to whole blood supplies as a source for treating combat casualties. In the military, 80 to 90 percent of casualties are lost before arriving at a hospital. Program researchers are looking to optimize advanced or "second generation" oxygen-carrying blood substitute products that have not yet been evaluated for militarily relevant applications through a series of simulation models.

The program recently signed a cooperative research and development agreement (CRADA) for a multi-center Phase II-B clinical trial, rolling into a definitive trial, to study blood substitutes in a civilian hospital setting. This novel collaboration brings together the military, private sector, and academicians. NMRC researchers will work with BioPure Corporation, the Society for the Advancement of Blood Management (SABM), U.S. Air Force, University of Maryland Shock Trauma, Yale University School of Medicine, and Dallas Parkland Hospital, to evaluate BioPure's HBOC –201 (an experimental product derived from cow's blood) for FDA approved military use. The trial will also establish multi-center clinical trial capability, a first for the military.

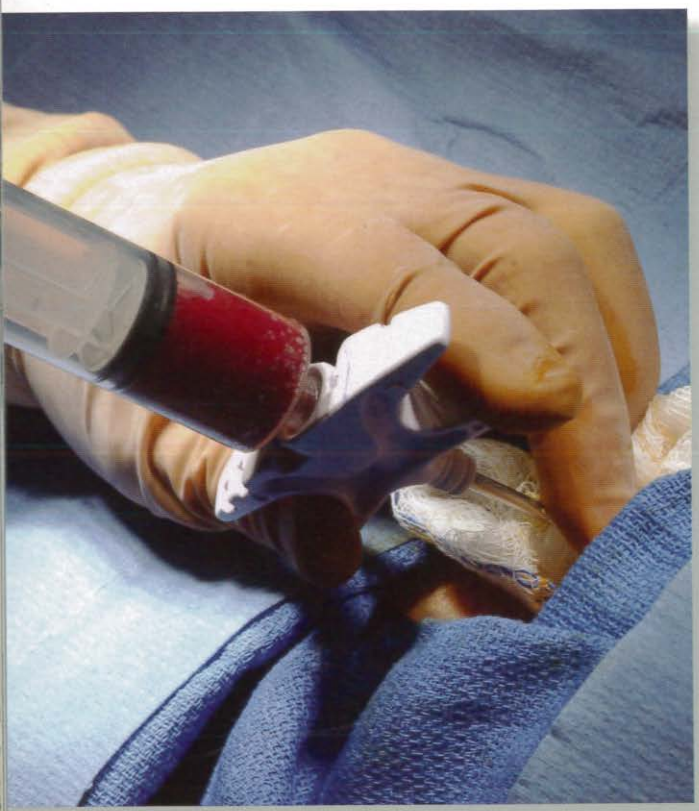
Researchers are also taking a basic science approach to the challenge of maintaining proper blood supplies in combat operations by developing a multifunctional blood substitute (MBS), a resuscitative fluid that simulates the function of whole blood, that can be injected systemically. The challenge in developing a viable product is to address the reasons why people die from hemorrhagic shock. It's expected to go to clinical trials within two years.


Bone Marrow Registry

C. W. BILL YOUNG MARROW DONOR PROGRAM

NMRC's C.W. Bill Young Marrow Donor Program (BYMDP) is a prime example of the Navy's innovative research and how it has far-reaching effects. What started as basic research to explore the idea of viable versus non-viable organ transplants has spawned a national registry of bone marrow donor candidates, giving the gift of life to service members and civilians.

C. W. BILL YOUNG MARROW DONOR PROGRAM



Exposure to radiation and chemical agents (such as nerve and mustard gases) used in modern warfare can cause unrecoverable damage to bone marrow (the blood-forming organ), breaking down the immune system in the process.

The idea of transplanting a viable organ like bone marrow, versus a non-viable organ, was revolutionary until the late1960's. When introduced, the concept opened the whole question of how the immune system works, a question that still continues today. Investigators are trying to identify how to strike a balance between keeping a transplant going without risking infection and the possible onset of other diseases.

GIVEN THE INCREASED RISK OF CHEMICAL ATTACKS DURING MILITARY CONFLICTS, IT IS CRUCIAL TO FIND WAYS TO TREAT POTENTIAL CASUALTIES OF WAR AND IMPROVE THEIR CHANCES FOR SURVIVAL.

In viable solid organ transplantation, the biggest concern is whether or not the patient's body will reject the organ. In which case a pathological condition can occur called graft versus host disease where cells from the transplanted tissue of a donor spark an immunologic attack on the cells and tissue of the recipient. In bone marrow transplants, the opposite scenario occurs because you take a more normal immune system from the transplant and put it into a recipient whose immune system is paralyzed. And so the organ can reject the person, making it even more critical to find the perfect match in donor marrow.

For more than 35 years, Navy investigators have focused their research on the set of genes that influence whether an organ transplant is accepted or rejected (especially bone marrow). The gene set of greatest concern in marrow transplants is called Human Leukocyte Antigen (HLA). Military casualties may be rescued using HLA matched platelets and in the most severe cases, marrow donations.

Managed by the Naval Medical Research Command, DoD's BYDMP was founded in 1985. It is named for Rep. C. W. Bill Young (FL-R), who lobbied Congress to initiate a national registry for bone marrow donors. In 1991, the Department of Health and Human Services assumed management of the civilian portion of the registry and it was officially named the National Marrow Donor Program (NMDP).

BYMP's mission in the treatment of radiation and chemical weapon exposure is unique to the Armed Forces. Identifying donors and receiving platelets or marrow donations can be a matter of days rather than months. However, because marrow transplantation is also instrumental in the treatment of cancer, the benefits of BYMP's research and data collection efforts continue to spill over into the civilian community. Today, the Navy still maintains data and recruits volunteer donors within the military community under BYMDP. About 12% (more than 300,000) bone marrow donors are registered through the DoD program. Participants may be selected as donors to fellow service members and their families as well as civilians.

Sailor Gets the Call

Jim was a 23-year old sailor attending the Navy's Hospital Corps School when he volunteered to join the DoD Marrow Donor Registry. Seven years later Jim, then a full time student in Corpus Christi, TX, was notified by the C.W. Bill Young / DoD Marrow Donor Center that he was the best match for a patient who needed a marrow transplant. Even after a seven-year wait, Jim did not hesitate to agree to continue his participation in the program. "It is a chance, to give someone a second shot at life", said Jim. "I've always supported the idea of transplant donations."

So Jim and his wife Michelle, with family members watching their two daughters, flew out to Washington, DC and checked into the Georgetown University Medical Center's Lombardi Cancer Center. There, Jim underwent the minor surgical procedure where, under anesthesia, doctors inserted a syringe through the pelvic bone and into a pool of marrow and extracted this lifesaving fluid. Over the next few weeks, the soreness in his lower back began to disappear and his body regenerated the marrow he gave.

Over a 12 month period, Jim received periodic updates on the condition of his recipient. What would he say to the recipient if he could talk to them right now? "It is my honor to do this, you are in our prayers."

NAVAL INSTITUTE FOR DENTAL AND BIOMEDICAL RESEARCH (NIDBR)

Since 1948, the Naval Institute for Dental and Biomedical Research (NIDBR), located on the Naval Station Great Lakes, Illinois, has been dedicated to researching problems related to oral health, wellness, disease and injury to increase operational readiness, address emergent dental problems, and enhance the health care delivery for military personnel.

In recent years, the Institute has expanded its scope beyond the clinical sciences, leveraging its expertise in oral biology, microbiology and bioenvironmental sciences to become an integral part of NMRC's worldwide network of state-of-the-art research laboratories. NIDBR's clinical, laboratory and bioenvironmental studies provide a comprehensive analysis of issues relevant to military health.

RESEARCH FOCUSES ON DEVELOPING SPECIFIC MATERIALS, DIAGNOSTIC TOOLS, AND BIOMETRICS TO IMPROVE THE DENTAL HEALTH AND READINESS OF SAILORS AND MARINES.

Research focuses on developing specific materials, diagnostic tools, and biometrics to improve the dental health and readiness of the fleet. The Institute monitors the operational impact of dental emergencies and collects longitudinal data related to oral disease trends, treatments, outcomes, and the origin of dental/maxillofacial emergencies.

Prevention assessment is a key component of NIDBR's epidemiological studies. Investigators develop evidence-based assessment tools to help identify military personnel who may be at high risk for experiencing acute dental problems. Using multivariate statistical methods, investigators redefine military dental readiness standards based on demographics, evidence-based risk assessment tools and dental health behaviors.

Researchers are currently testing mobile dental delivery systems for use by the Fleet Marine Force in deployed environments, as well as evaluating a dental triage, diagnosis and treatment CD-ROM for dental emergencies. Investigators are also developing an innovative dental dressing that can be used by non-dental personnel to stabilize dental emergencies in remote areas and in combat situations until the patient is able to receive definitive care. In a related project, NIDBR researchers are looking at the potential to develop a synthetic skin for repairing facial damage resulting from severe combat trauma.

Another key component of the Institute's investigations is the development of diagnostic technologies for non-invasive detection of militarily relevant infectious diseases and biological warfare agents. These laboratory studies center on the developing of diagnostic screening tests for detecting infectious diseases (such as tuberculosis, dengue fever, etc.) and determining immunization status. The tests are non-invasive, rapid (take five minutes or less) and use oral fluid (saliva), providing ease of use for militarily relevant applications. Investigators are currently testing two experimental assays, one to evaluate the immunization status of military personnel who have received the anthrax vaccine and another to diagnose pulmonary tuberculosis.

To complement its findings in clinical and laboratory studies, NIDBR is also engaged in the very important work of evaluating the environmental impact of dental treatment. Heavy metal contamination of the dental-unit wastewater stream and biofilm accumulations in dental-unit water supply tubing can adversely affect the environment and safety of patients and providers.

The Institute maintains a Web site (www.dentalmercury.com) as a training resource for the management of dental mercury in the dental-unit wastewater stream. As the lead agent for the Navy's Dental Mercury Abatement Program, researchers are evaluating pretreatment methods and technologies to remove mercury from the wastewater stream before it reaches local sanitary systems. Parallel studies are examining technologies to prevent biofilms from forming in dental-unit water lines and preventing chemical interactions with other dental treatment by-products.

NAMRU-2
JAKARTA, INDONESIA

The U.S. Naval Medical Research Unit No. 2 (NAMRU-2) supports the U.S. Forces in the Pacific Theater by studying military relevant infectious disease threats in both active duty and civilian populations. Itt is WHO Collaborating Center for emerging infectious diseases.

NAMRU-2 provides the Navy and Marine Corps with a continued forward presence that combines virology, microbiology, epidemiology, immunology parasitology, entomology, and clinical medicine into a comprehensive capability to study tropical diseases where they occur. Only in this environment can new preventive measures and treatments be tested and evaluated to improve the health of the local civilian population and the operational readiness of deployed U.S. Forces.

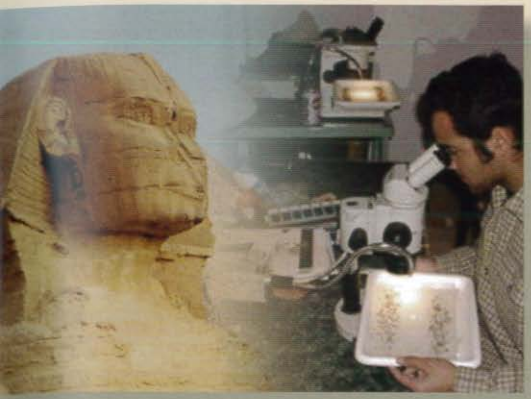
NAMRU-2 has strong ties with the Indonesia Ministry of Health, the Indonesian Center for Disease Control, and the Indonesian National Institute of Health Research and Development. These research affiliations, coupled with a high incidence of tropical infectious disease problems in reasonably accessible areas, have led to an increasing role for NAMRU-2 in joint U.S.-Indonesia endeavors.

NAMRU-2 has expanded surveillance efforts to other countries in Southeast Asia including Vietnam, Laos, Singapore, Philippines, Thailand, and Cambodia. In Phnom Penh, Cambodia, NAMRU-2 has opened, outfitted, and staffed a satellite laboratory to conduct regional infectious disease outbreak surveillance and diagnostic laboratory support.

NAMRU-3
CAIRO, EGYPT

The U.S. Naval Medical Research Unit No. 3 (NAMRU-3) conducts research and surveillance to support military personnel deployed to Africa, the Middle East, and Southwest Asia. The mission also includes the evaluation of vaccines, therapeutic agents, diagnostic assays, and vector control measures.

NAMRU-3 is adjacent to the Abbassia Fever Hospital, the oldest and largest fever hospital in the Middle East. NAMRU-3 has modern research laboratories, a medical research library, and is the only laboratory in Africa with an animal facility accredited by the American Association for Accreditation of Laboratory Animal Care. It is the largest DoD overseas laboratory, with BSL-3 bio-containment space and field and hospital study sites located throughout Egypt. A malaria field site is located in the upper east region of northern Ghana.



NAMRU-3 works closely with the Egyptian Ministry of Health and Population, the U.S. National Institutes of Health, the World Health Organization, the U.S. Agency for International Development and the U.S. Centers for Disease Control and Prevention. NAMRU-3 is a WHO Collaborating Center for HIV and Emerging Infectious Diseases.

NAMRU-3 established a presence in Egypt in 1942 when the U.S. Typhus Commission placed a research laboratory staffed by American scientists and technicians in Cairo. The laboratory played a major role in averting a serious typhus outbreak during and following World War II. After the war, the Navy was invited by the Egyptian Government to continue collaborative studies of endemic tropical and subtropical diseases. In response, NAMRU-3 was formally established in 1946.

NMRCD
PERU, SOUTH AMERICA

Hosted by the Peruvian Navy and co-located at their flagship hospital in Lima, the Naval Medical Research Center Detachment (NMRCD) conducts research on and surveillance of a wide range of infectious diseases that threaten military operations in the region. These include malaria and dengue fever, yellow fever, viral encephalitides, leishmaniasis, Chagas' disease, and enteric diseases such as shigellosis and typhoid fever.

NMRCD partners with the Peruvian Army and Navy, and works closely with prestigious universities like Cayetano-Heredia and San Marcos. NMRCD enjoys a close and productive relationship with the Ministry of Health, and collaborates with USAID, US CDC, US NIH, PAHO, and a number of American universities.

These partnerships yeild a robust research agenda that includes prevention strategies, clinical management and trials, chemotherapeutics, immuno- and molecular rapid diagnostics, epidemiology, ecology, as well as social and economic impact.

Since its inception in 1983, NMRCD has capitalized its access to infectious disease threats endemic to South America through strong institutional partnerships. The disease surveillance programs engage more than two dozen instututions in ten South American nations. For example, NMRCD and its partners were the first to detect HIV genotype-F in Peru and Paraguay and genotype-A in Peru. Using its permanent field laboratory and staff at Iquitos on the Amazon River in eastern Peru, NMRCD worked with numerous collaborators to document the spread of dengue fever and its vectors through the Amazon River basin.

NMRC IN PARTNERSHIP WITH PRIVATE INDUSTRY

Through an active technology transfer program, NMRC's Office of Technology Transfer (OTT) facilitates Cooperative Research and Development Agreements (CRADAs) and Material Transfer Agreements (MTAs) between private organizations and all NMRC laboratories. NMRC leverages its scientific talent and resources by working in close collaboration with private companies, universities, and medical centers to move promising technologies from the bench to the battlefield and bedside.

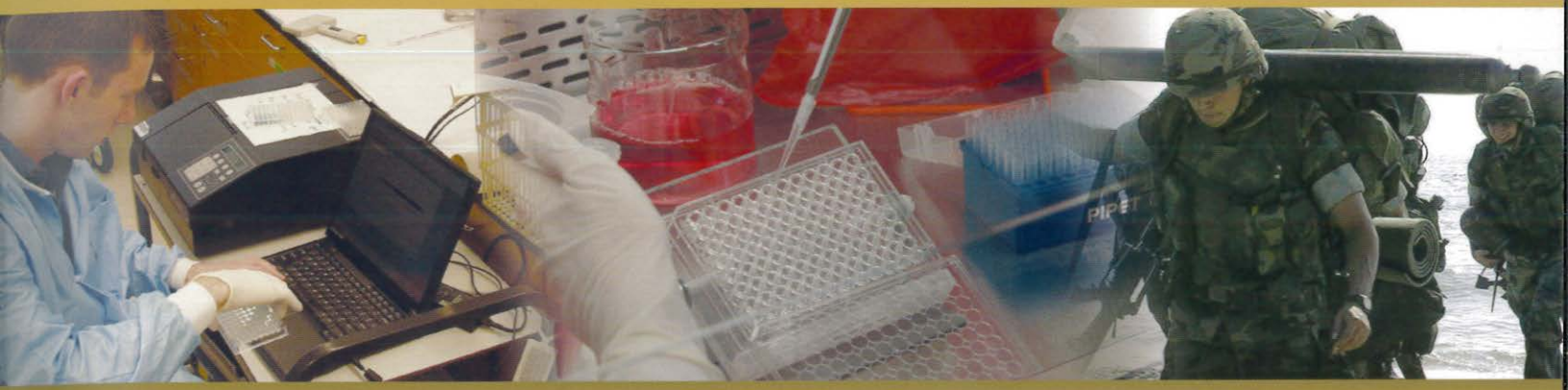
A good example of this would be a recent CRADA with a private company to conduct Phase III clinical trials of a new chemically modified hemoglobin solutions. Hemorrhage accounts for the preponderance of potentially salvageable combat casualty mortalities and is a large contributor to deaths in civilians where there is a long pre-hospital time frame. It is thus paramount to maximize resuscitative techniques that address these injuries. The current standard of care in the field or pre-hospital setting relies on hemostasis, fluid resuscitation, and evacuation. Although blood transfusion may be lifesaving, the capability is costly and sometimes unavailable. A safe and efficacious oxygen carrying resuscitative fluid that can augment microcirculatory flow and increase tissue oxygenation is urgently needed to decrease potentially avoidable fatalities.

Hemoglobin based oxygen carriers (HBOCs) are chemically modified hemoglobin solutions that may be room temperature stable with a long shelf life, may be free of communicable pathogens, and have no ABO/Rh or other blood antigens. Research suggests that HBOCs are likely to improve cardiovascular parameters and tissue perfusion, reverse anaerobic metabolism, and decrease morbidity and mortality. Hemoglobin substitutes are potentially ideal resuscitative fluids for hemorrhagic shock casualties.

Hemopure® is the trademark for an ultrapure, bovine-derived, polymerized hemoglobin solution with a hemoglobin concentration of 13 g/dL and an osmotic pressure similar to whole blood. The source of bovine hemoglobin is controlled herds with known origins and medical histories. Hemopure on-loads and off-loads oxygen and appears safe in animal and human studies. Hemopure has been utilized in 22 clinical trials, including a Phase III trial in patients undergoing orthopedic surgery that included stabilized trauma patients, and the results of some of the other clinical trials of Hemopure have been published in peer-reviewed journals.

When technologies are transferred to the competitive marketplace, OTT also offers marketing support and negotiates licensing on behalf of investigators. These collaborative relationships help accelerate the development of promising medical technologies.

The Command currently has 26 patent applications pending at the U.S. Patent and Trademark Office and 49 issued patents. These include DNA-based vaccines for dengue fever, malaria, and anthrax. Many of these technologies have been licensed and are in various stages of clinical development. NMRC also has a large portfolio of technologies currently available for licensure.



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